CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214628Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 12, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214628
Product Name and Strength:	Norepinephrine in Sodium Chloride Injection, 4 mg/250 mL (16 mcg/mL), 8 mg/250 mL (32 mcg/mL), and 16 mg/250 mL (64 mcg/mL)
Applicant/Sponsor Name:	Nevakar Injectables, Inc.
OSE RCM #:	2017-1712-4
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on September 2, 2022 for Norepinephrine in Sodium Chloride Injection. We reviewed the revised container label and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Mehta, H. Label and Labeling Review for Norepinephrine in Sodium Chloride (NDA 214628). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUL 12. RCM No.: 2017-1712-3.

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HINA S MEHTA
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	July 12, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214628
Product Name, Dosage Form, and Strength:	Norepinephrine in Sodium Chloride Injection 4 mg/250 mL (16 mcg/mL), 8 mg/250 mL (32 mcg/mL), and 16 mg/250 mL (64 mcg/mL)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Nevakar Injectables, Inc.
FDA Received Date:	April 8, 2022
OSE RCM #:	2020-1712-3
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process of the 505(b)(2) NDA class 2 resubmission for Norepinephrine in Sodium Chloride Injection, we reviewed the proposed prescribing information (PI), container labels, and overwrap labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND INFORMATION

Nevakar Injectables, Inc. submitted Norepinephrine in Sodium Chloride Injection (NDA 214628) on August 17, 2020, a 505(b)(2) application which relies on the Listed Drug (LD) Levophed (norepinephrine bitartrate) Injection. Levophed Injection is currently approved as a 4 mg/4 mL (1 mg/mL) single-dose vial or single-dose ampule which requires dilution in 1,000 mL of 5% Dextrose or 5% Dextrose/Sodium Chloride for intravenous infusion. We previously reviewed the label and labeling.[abc] However, the application received a complete response on June 14, 2021 for facility deficiencies.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

[a] Aidoo, M. Label and Labeling Review for Norepinephrine in Sodium Chloride (NDA 214628). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 24. RCM No.: 2020-1712.
[b] Aidoo, M. Label and Labeling Review for Norepinephrine in Sodium Chloride (NDA 214628). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 14. RCM No.: 2020-1712-1.
[c] Aidoo, M. Label and Labeling Review for Norepinephrine in Sodium Chloride (NDA 214628). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 24. RCM No.: 2020-1712-2.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the full prescribing information (PI), container and overwrap labels to identify deficiencies that may lead to medication errors and areas for improvement.

We note Section 16 of the PI states the product will be available in (b) (4). This terminology may be cause confusion and we provide recommendations for the Division. The labeling submitted did not include the 10-bag carton labeling. We request the Applicant submit this labeling for our review. Our review of the container labels and overwrap labeling found inconsistency with the storage statement when compared to the PI.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI, container labels, and overwrap labels can be improved to increase clarity of information. We provide recommendations for the Division in Section 4.1 and for Nevakar in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Prescribing Information

1. How Supplied/Storage and Handling Section

   a. As currently presented, the terminology (b) (4) in the last column of the how supplied table may cause confusion. We recommend revising (b) (4) to "Package Size" and (b) (4) to "10 bags" for clarity on how the carton is supplied.

4.2 RECOMMENDATIONS FOR NEVAKAR INJECTABLES, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Overwrap and Container labels)

1. The storage information is lacking information on the excursions that are permitted. We recommend revising the storage statement to include the excursions permitted for consistency with the prescribing information.

B. Carton Labeling

1. We note that each strength of the proposed product will be supplied in a carton of 10 x 250 mL bags. We recommend you submit the carton labeling for our review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Norepinephrine in Sodium Chloride received on April 8, 2022 from Nevakar Injectables, Inc..

Table 2. Relevant Product Information for Norepinephrine in Sodium Chloride and the Listed Drug		
Product Name	Norepinephrine in Sodium Chloride	Levophed[d] [NDA 007513 – Hospira Inc]
Initial Approval Date	N/A	July 13, 1950
Active Ingredient	Norepinephrine in Sodium Chloride	Norepinephrine Bitartrate
Indication	Restoration of blood pressure in adult patients with acute hypotensive states.	Restoration of blood pressure in adult patients with acute hypotensive states.
Route of Administration	(b) (4) intravenous infusion	(b) (4) intravenous infusion.
Dosage Form	Injection	Injection
Strength	4 mg/250 mL (16 mcg/mL), 8 mg/250 mL (32 mcg/mL), and 16 mg/250 mL (64 mcg/mL)	4 mg/4 mL (1 mg/mL) norepinephrine base in single-dose glass vial or ampule.
Dose and Frequency	• Initial intravenous infusion rate of 8 mcg to 12 mcg of base per minute, adjust the rate of flow to establish and maintain a low to normal blood pressure (usually 80 mm Hg to 100 mm Hg) sufficient to maintain the circulation of vital organs. • Maintenance dose: 2 mcg to 4 mcg of base per minute.	• Initial dose of 0.25 mL to 0.375 mL (from 8 mcg to 12 mcg of base) per minute. Adjust the rate of flow to establish and maintain a low to normal blood pressure (usually 80 mm Hg to 100 mm Hg systolic) sufficient to maintain the circulation of vital organs. • Maintenance dose: 0.0625 mL to 0.125 mL per minute

[d] Levophed [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2020 OCT 20. Available from: https://www.accessdata.fda.gov/spl/data/3652a10f-51e3-4906-b85f-7e4518ac14a6/3652a10f-51e3-4906-b85f-7e4518ac14a6.xml

		(from 2 mcg to 4 mcg of base)
How Supplied	Each carton contains 10 x 250 mL infusion bags packaged in an aluminum overwrap.	Each carton contains 10 ampules or 10 vials.
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.] Protect from light.	Store between 20°C and 25°C (68° and 77°F) ; excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.]Protect from light.
Container Closure	Single-dose, ready-to-use non-PVC infusion bag in an aluminum foil pouch.	Glass vial or ampule

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 5, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Norepinephrine'. Our search identified three previous reviews[e,f,g], and we considered our previous recommendations to see if they are applicable for this current review.

[e] Aidoo, M. Label and Labeling Review for Norepinephrine in Sodium Chloride (NDA 214628). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 24. RCM No.: 2020-1712.

[f] Aidoo, M. Label and Labeling Review for Norepinephrine in Sodium Chloride (NDA 214628). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Jan 14. RCM No.: 2020-1712-1.

[g] Aidoo, M. Label and Labeling Review for Norepinephrine in Sodium Chloride (NDA 214628). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 24. RCM No.: 2020-1712-2

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[h] along with postmarket medication error data, we reviewed the following Norepinephrine in 0.9% Sodium Chloride Injection labels and labeling submitted by Nevakar Injectables, Inc..

- Container labels received on April 8, 2022
- Overwrap labeling received on April 8, 2022
- Prescribing Information (Image not shown) received on April 8, 2022, available from \\CDSESUB1\evsprod\nda214628\0018\m1\us\114-labeling\draft\labeling\norepinephrine-prescribing-information-clean-pdf.pdf

[h] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 11, 2022

To: Quynh Nguyen, Regulatory Project Manager
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda Wilson, Team Leader, OPDP

Subject: OPDP Labeling Comments for OPDP Labeling Comments for Norepinephrine in Sodium Chloride Injection, for intravenous use

NDA: 214628

In response to DCN's consult request dated April 28, 2022, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Norepinephrine in Sodium Chloride Injection, for intravenous use. This supplement provides for a new application indicated for restoration of blood pressure in adult patients with acute hypotensive states.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DCN on July 7, 2022, and we have no additional comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 8, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meena Savani at (240) 402-1348 or Meena.Savani@fda.hhs.gov.

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MEENA R SAVANI
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 24, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214628
Product Name and Strength:	Norepinephrine in Sodium Chloride Injection 4 mg/250 mL (16 mcg/mL), 8 mg/250 mL (32 mcg/mL), 16 mg/250 mL (64 mcg/mL)
Applicant/Sponsor Name:	Nevakar, Inc.
OSE RCM #:	2020-1712-2
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on January 29, 2021 for Norepinephrine in Sodium Chloride Injection. We review the revised container labels and carton labeling for Norepinephrine in Sodium Chloride Injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Aidoo, M. Label and Labeling Review for Norepinephrine in Sodium Chloride Injection (NDA 214628). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 20. RCM No.: 2020-1712-1.

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/s/

MARIETTE A AIDOO
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HINA S MEHTA
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 12, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214628
Product Name and Strength:	Norepinephrine in Sodium Chloride Injection 4 mg/250 mL (16 mcg/mL), 8 mg/250 mL (32 mcg/mL), 16 mg/250 mL (64 mcg/mL)
Applicant/Sponsor Name:	Nevakar, Inc.
OSE RCM #:	2020-1712-1
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on January 4, 2021 for Norepinephrine in Sodium Chloride Injection. We review the revised container labels and carton labeling for Norepinephrine in Sodium Chloride Injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling is unacceptable from a medication error perspective. Inconsistencies exist between the carton versus container labels in terms of the depiction (b) (4) as well as the incongruent color coding depicted per each strength on the principal display panel of the carton labeling.

3 RECOMMENDATIONS FOR NEVAKAR, INC.

We recommend the following be implemented prior to approval of this NDA:

[a] Aidoo, M. Label and Labeling Review for Norepinephrine in Sodium Chloride Injection (NDA 214628). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 20. RCM No.: 2020-1712.

A. Carton Labeling
    a. Per the draft guidance Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products – Content and Format (line 1078-81), the concentration of the vehicle named in the official title is stated as part of the official title on the container label and carton labeling. Revise the carton labeling from (b) (4) to "Norepinephrine in 0.9% Sodium Chloride Injection".
    b. We note the use of the (b) (4) bar in the lower portion of the PDP for the carton labeling to highlight different product strengths. In addition, (b) (4) purple color is used to depict the font color for the 8 mg per 250 ml strength. The use of (b) (4) color of the font of one strength and (b) (4) border color on the other strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors. Consider revising the border color at the bottom of the label to match the font color for each strength, i.e. green border color for the Norepinephrine 16 mcg/mL and a blue border color for Norepinephrine 64 mcg/mL bags.

B. Container Labels
    a. The usage of symbols and abbreviations can cause misinterpretation and confusion.[b] We note the use of the abbreviation "IV" on the container labels. Please revise statement to "Use optimal intravenous access (largest vein possible) to minimize risk of extravasation."

[b] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 Sep 16]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 11, 2020

To: Quynh Nguyen, Regulatory Project Manager
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for Norepinephrine in Sodium Chloride Injection, for intravenous use

NDA: 214628

In response to the Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology's (DRO-CHEN) consult request dated September 9, 2020, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Norepinephrine in Sodium Chloride Injection, for intravenous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DRO-CHEN (Quynh Nguyen) on November 30, 2020 and we have no additional comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor on August 17, 2020 and received by electronic email from DRO-CHEN (Quynh Nguyen) on November 30, 2020 and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at (301) 796-1233 or Carrie.Newcomer@fda.hhs.gov.

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CARRIE A NEWCOMER
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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Date of This Review:	November 20, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214628
Product Name, Dosage Form, and Strength:	Norepinephrine in Sodium Chloride Injection 4 mg/250 mL (16 mcg/mL), 8 mg/250 mL (32 mcg/mL), 16 mg/250 mL (64 mcg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:0	Prescription (Rx)
Applicant/Sponsor Name:	Nevakar, Inc.
FDA Received Date:	August 17, 2020 and October 29, 2020
OSE RCM #:	2020-1712
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As a part of the approval process for 505(b)(2) NDA 214628 submission, this review evaluates the proposed Prescribing Information (PI) and carton and container labels for Norepinephrine in Sodium Chloride Injection.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Nevakar submitted a 505(b)(2) NDA to obtain marketing approval for Norepinephrine Bitartrate in Sodium Chloride Injection. The Listed Drug (LD) for this product is Levophed (norepinephrine bitartrate) Injection. Levophed Injection is currently approved as a 4 mg/4 mL (1 mg/mL) single-dose vial or single-dose ampule that is diluted in 1,000 mL of 5% Dextrose or 5% Dextrose/Sodium Chloride for intravenous infusion. We note Levophed and the proposed Norepinephrine Bitartrate in Sodium Chloride will have the same indication, route, and dosing regimen. However, there are differences in the proposed presentation as Norepinephrine Bitartrate in Sodium Chloride will be available in 4 mg/250 mL (16 mcg/mL), 8 mg/250 mL (32 mcg/mL) and 16 mg/250 mL (64 mcg/mL) as premixed, ready-to-use intravenous infusion bags.

We performed a risk assessment of the full prescribing information (PI), carton and container labels to identify deficiencies that may lead to medication errors and areas for improvement. For the Division, we note the PI could be improved for clarity with respect to the appropriate package type term and the OPQ determined salt amounts based on the salt equivalency policy. For the Applicant, we note inconsistency in the presentation of the strength in relation to the PI, and revision of storage information to ensure consistency with the PI. We provide

recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 below and advise they be implemented prior to approval of NDA 214628.

4 CONCLUSION & RECOMMENDATIONS

Our review concludes the proposed PI, carton and container labels for Norepinephrine in 0.9% Sodium Chloride Injection may be improved to ensure safe product use. We provide specific recommendations for the Division in Section 4.1 and recommendations for Nevakar in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Highlights of Prescribing Information

1. Dosage and Administration

    a. We recommend adding the statement "No further dilution prior to infusion is required (2.1)" to prevent any confusion as this product is in solution and ready for infusion.

B. Prescribing Information

1. Dosage and Administration, 2.1 Important Dosage and Administration Instructions

    a. Consider revising the last sentence of Administration to read: (b) (4) [redacted]

    b. At the end of the discontinuation section we recommend adding "Single dose only. Discard unused portion" to prevent confusion.

2. Dosage Form and Strengths

    a. As currently presented, "bitartrate" is not included as part of the established name throughout the proposed product labeling. We defer to OPQ to determine if the inclusion of "bitartrate" is appropriate as part of the established name and within the product strength statement throughout the product labeling.

3. How Supplied/Storage and Handling Section

    a. We recommend adding the description of the product and package type term to Section 16 to read as follows: " Norepinephrine in 0.9% Sodium Chloride Injection (norepinephrine bitartrate) is supplied as a *clear,*

colorless sterile solution in a 250 mL non-PVC *single-dose* infusion bag with single function connector system consisting of a port and cap, packaged individually in an aluminum foil pouch with an oxygen scavenger."

b. Consider revising the statement (b) (4) to read: "Protect from light. Keep in (b) (4) overwrap until ready to use. Discard after 24 hours of opening overwrap" for increased clarity.

4.2 RECOMMENDATIONS FOR NEVAKAR, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. As currently presented the route of administration is presented as (b) (4) and it is not prominent. We recommend replacing the statement (b) (4) (b) (4) with "For Intravenous Infusion Only" to prevent confusion. In addition, remove (b) (4) that is listed on the left corner of the labels and labeling.
2. Consider placing the statements "Single dose container" and "Discard unused portion" right next to each other for clarity.
3. Consider keeping the statements: "Stable out of overwrap for 24 hours | Do not use if solution is discolored" in the same chronological order on both the container and the carton label to ensure consistency. Alternatively: consider revising the statement above to read: (b) (4) for increased clarity and conciseness.

B. Carton Labeling

1. Consider including the statement "Protect from light" as part of the storage information for consistency with the PI label.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Norepinephrine in Sodium Chloride Injection received on August 17, 2020 and October 29, 2020 from Nevakar, Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Norepinephrine in Sodium Chloride Injection and the Listed Drug

Product Name	Norepinephrine in Sodium Chloride Injection	Levophed[a] [NDA 007513 – Hospira Inc]
Initial Approval Date	N/A	July 13, 1950
Active Ingredient	Norepinephrine bitartrate	Norepinephrine Bitartrate
Indication	To raise blood pressure in adult patients with severe, acute hypotension.	(b) (4)
Route of Administration	(b) (4) intravenous infusion	Repeated intravenous injection, or (b) (4) infusion.
Dosage Form	injection	Injection
Strength	4 mg/250 mL (16 mcg/mL), 8 mg/250 mL (32 mcg/mL), 16 mg/250 mL (64 mcg/mL)	4 mg/4 mL (1 mg/mL) norepinephrine base in single-dose glass vial or ampule.
Dose and Frequency	Initial intravenous infusion rate of 8 mcg to 12 mcg of base per minute, adjust the rate of flow to establish and maintain a low to normal blood pressure (usually 80 mm Hg to 100 mm Hg) sufficient to maintain the circulation of vital •Maintenance dose: 2 mcg to 4 mcg of base per minute.	Initial dose of 0.25 mL to 0.375 mL (from 8 mcg to 12 mcg of base) per minute. Adjust the rate of flow to establish and maintain a low to normal blood pressure (usually 80 mm Hg to 100 mm Hg systolic) sufficient to maintain the circulation of vital organs. •Maintenance dose: 0.0625 mL to 0.125 mL per minute (from 2 mcg to 4 mcg of base)

[a] Levophed [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2020 OCT 20. Available from: https://www.accessdata.fda.gov/spl/data/3652a10f-51e3-4906-b85f-7e4518ac14a6/3652a10f-51e3-4906-b85f-7e4518ac14a6.xml

How Supplied	Each carton contains one 250mL infusion bag packaged in an aluminum over wrap.	1 box of 10 ampules or 10 vials in a carton
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.] Protect from light.	(b) (4) Protect from light.
Container Closure	Single-dose, ready-to-use non-PVC infusion bag in an aluminum foil pouch.	Glass vial or ampule

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 29, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, norepinephrine. Our search identified one previous reviews[b], and we considered our previous recommendations to see if they are applicable for this current review.

[b] Aidoo, M. Label and Labeling Review for Norepinephrine Bitartrate (NDA 214313). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 17. RCM No.: 2020-513.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Norepinephrine in Sodium Chloride Injection labels and labeling submitted by Nevakar, Inc.

- Container label received on August 17, 2020
- Carton labeling received on August 17, 2020
- Prescribing Information (Image not shown) received on August 17, 2020 and October 29, 2020, available from \\CDSESUB1\evsprod\nda214628\0001\m1\us\114-labeling\draft\labeling\norepinephrine-prescribing-information-pdf.pdf

G.2 Label and Labeling Images

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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